Is there a place for corifollitropin alfa in IVF/ICSI cycles? A systematic review and meta-analysis

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Objective: To evaluate the role of corifollitropin alfa, a newly developed weekly administrated long-acting recombinant FSH (rFSH), as an alternative for daily rFSH administration in women undergoing controlled ovarian stimulation in GnRH antagonist down-regulated in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment cycles.

Design: Systematic review and meta-analysis of randomized controlled trials.

Setting: University and private centers.

Patient(s): Infertile women undergoing IVF/ICSI treatment.

Intervention(s): Comparing long-acting rFSH corifollitropin alfa versus standard daily administrated rFSH in GnRH antagonist IVF/ICSI cycles.

Main Outcome Measure(s): Ongoing pregnancy rate, live birth rate, clinical pregnancy rate, miscarriage rate, duration of stimulation, amount of FSH, number of retrieved oocytes, number of mature oocytes, number of embryos obtained, fertilization rate, ovarian hyperstimulation syndrome (OHSS) incidence, and adverse events.

Result(s): Four randomized trials involving 2,326 women were included. There was no evidence of a statistically significant difference in ongoing pregnancy rate for corifollitropin alfa versus rFSH. There was evidence of increased ovarian response and risk of OHSS in corifollitropin alfa.

Conclusion(s): In view of its equivalence and safety profile, corifollitropin alfa in combination with daily GnRH antagonist seems to be an alternative for daily rFSH injections in normal responder patients undergoing ovarian stimulation in IVF/ICSI treatment cycles. (Fertil Steril® 2012;97:876–85. ©2012 by American Society for Reproductive Medicine.)

Key Words: Corifollitropin alfa, FSH-CTP, follicle stimulating hormone—C-terminal peptide, Org 36286, Org36286, Org-36286, rFSH, meta-analysis, IVF, ICSI

A part of in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment, controlled ovarian stimulation (COS) with gonadotropins during each cycle is the first step. Traditionally, hMG, highly purified FSH, or recombinant FSH (rFSH) injections are used. These injections have to be administered daily to maintain adequate levels of FSH during COS, because of their short elimination half-life and rapid metabolic clearance (1).

Long-acting rFSH—corifollitropin alfa—has recently become available. Corifollitropin alfa is a new hybrid molecule with sustained follicle-stimulating activity; it has a longer half-life, interacting only with FSH receptors without LH activity, which provides a plasma half-life of ~65 hours (2–5). Corifollitropin alfa comprises an alpha-subunit, which is identical to that of FSH, and a beta-subunit, which is produced by the fusion of the C-terminal peptide from the beta-subunit of hCG to the beta-subunit of FSH (6, 7). The optimal corifollitropin dose has been calculated to be 100 µg for women with a body weight ≤60 kg and 150 µg for women with a body weight >60 kg (8, 9). From phase II and III studies it was concluded that a single injection of corifollitropin alfa can replace the first seven injections with standard daily gonadotropins and that stimulation can be continued with daily FSH injections if the need arises (9). This makes corifollitropin alfa potentially more patient-friendly and may lead to a lower dropout rate of patients (10), if safety and effectiveness are first demonstrated. The present review summarizes the evidence from randomized controlled studies (RCTs) on effectiveness, safety, and toleration of corifollitropin alfa and rFSH, in IVF or ICSI cycles.

METHODS

Search Strategy for Identification of Studies

The following electronic databases were searched: Medline, Embase, Science
Direct, Cochrane Central Registry of Controlled Trials (Central), Web of Science, National Research Registry (NRR), and Medical Research Council’s Clinical Trials Registry. A search strategy was carried out based on the following terms: long-acting FSH, corifollitropin alfa, FSH, hMG, IVF, ICSI, AND live birth rate, ongoing pregnancy rate, and ovarian hyperstimulation syndrome; chorionic; safety; tolerance AND “randomized controlled trial(s)” OR “randomised controlled trial(s).” Furthermore, we examined the reference lists of all known primary studies, review articles, citation lists of relevant publications, abstracts of major scientific meetings (e.g., European Society for Human Reproduction and Embryology and European Society for Reproductive Medicine) and included studies to identify additional relevant citations. In addition, references from all identified articles were checked, and a hand search of the abstracts from the annual meetings of the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology was performed. The search was not restricted by language. The searches were conducted independently by M.A.Y. and W.K.

**Study Selection and Data Extraction**

Studies were selected if the target population consisted of subfertile couples with any cause and the therapeutic interventions were corifollitropin alfa versus rFSH in IVF or ICSI treatment. Studies had to be of randomized design. The primary outcome measure was ongoing pregnancy rate per randomized woman. Secondary outcomes were live birth rate, clinical pregnancy rate, early miscarriage rate per randomized woman, number of metaphase II (MII) oocytes per oocyte pick-up (OPU), number of embryos obtained and fertilization rate per patient with ICSI, OHSS incidence, adverse events, cycle cancellation, and total duration and amount of rFSH used and from day 8 onward.

Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by the two reviewers independently, and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Final inclusion or exclusion decisions were then made on examination of the full manuscripts. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer. The selected studies were assessed for methodologic quality by using the components of study design related to internal validity (11). Information on the adequacy of randomization, concealment, and blinding was extracted. From each study, outcome data were extracted in 2 × 2 tables. Data extraction was performed in duplicate by M.A.M.Y. and W.K.

**Statistical Analysis**

Dichotomous outcomes were expressed as an odds ratio (OR) with 95% confidence interval (CI) using a fixed effects model and a random effects model. All outcomes were calculated according to intention-to-treat analysis.

Where studies gave data on mean and range instead of standard deviation (SD), the SD was estimated to be approximately one-fourth of the typical range of data (Cochrane Handbook for Systematic Reviews of Intervention, version 5.02). All statistical analyses were performed with Rev-Man 5.0 (Cochrane Collaboration).

**RESULTS**

The search strategy yielded 31 publications related to the topic. Fourteen publications were excluded because they did not fulfill the selection criteria (Fig. 1). The excluded trials, with the main reasons for their exclusion, are presented in Table 1 (4, 6, 9, 10, 12–22). The included four trials enrolled 2,326 randomized women. The quality and the main characteristics of the included trials are presented in Table 2. The studies were generally large and well powered for the clinically relevant outcomes, with sample sizes varying from 99 to 1,506 women. Three studies were multicenter (Engage [3], Ensure [23], and Corifollitropin Alfa Dose-Finding Study Group [24]), two studies were double-blind, double-dummy, active-controlled, noninferiority-equivalent (Ensure and Engage). Two studies were phase III trials (Ensure and Engage), and two were phase II studies (Devroye et al. [25] and Corifollitropin Alfa Dose-Finding Study Group). All trials were sponsored or supported by the manufacturer of corifollitropin alfa (Schering-Plough). Two studies were two arms (Engage and Ensure), and the other two were four arms comparing different doses of corifollitropin alfa ranging from 60 to 240 μg. All trials were published as full text in peer-reviewed journals. All studies used a GnRH antagonist protocol for down-regulation. As GnRH antagonist, ganirelix (0.25 mg; Organon) was used in all

**FIGURE 1**

trials, and as rFSH follitropin beta Puregon/Follistim (Organon) was used with a dose ranging from 150 to 200 IU. One study included only patients with body weight >60 kg (Engage), and one study included only patients with body weight <60 kg (Ensure); the other two studies included patients with a body mass index between 17 and 31 kg/m².

Pregnancy Outcomes per Randomized Women

There was no evidence of a statistically significant difference in ongoing pregnancy rate (4 RCTs; OR 0.80, 95% CI 0.54–1.20) or in live birth rate (1 RCT; OR 1.15; 95% CI 0.99–1.41) between corifollitropin alfa compared with daily rFSH (Fig. 2A). Assuming an ongoing pregnancy rate of 36% after rFSH, this means that the corresponding ongoing pregnancy rate after corifollitropin alfa would be 33% (95% CI 26%–40%). The trials differed in effect size resulting in moderate heterogeneity (I² = 59%).

In the sensitivity analysis excluding the results of the two phase II trials (Devroey et al. and Corifollitropin Alfa Dose Finding Study Group), the OR for clinical pregnancy rate in ongoing pregnancy rate (4 RCTs; OR 0.92, 95% CI 0.79–1.15).

There was also no evidence of a difference in clinical pregnancy rate (3 RCTs; OR 0.92, 95% CI 0.69–1.25; no heterogeneity: I² = 0%). In the sensitivity analysis excluding the results of phase II trials, the OR for clinical pregnancy rate was similar (2 RCTs; OR 0.99, 95% CI 0.82–1.19).

Early Miscarriage per Woman Randomized

There was no evidence of a statistically significant difference in early miscarriage between both groups (3 RCTs; OR 1.07, 95% CI 0.59–1.94; P=.31; minor heterogeneity: I² = 16%).

Ovarian Stimulation Outcomes per Woman Randomized

Significantly less FSH was used in the corifollitropin alfa group (2 RCTs; WMD −1.227 IU, 95% CI −1.570 to −0.888; P<.00; extreme heterogeneity: I² = 98%) (Fig. 2B). The absolute total doses of rFSH ranged from 0 to 1,550 IU in the corifollitropin alfa group to 400–2,800 IU in rFSH.

Regarding the total dose of rFSH from day 8 onward, there was no significant difference between study groups (2 RCTs; WMD 5.36, 95% CI −33 to −44; P=.60; no heterogeneity: I² = 0%).

There was no evidence of a difference between both groups in duration of stimulation (2 RCTs; WMD 0.23–0.23; P=1.0; no heterogeneity: I² = 0%).

All trials reported on the number of retrieved oocytes, MII oocytes, and total number of obtained embryos. However, these data were typically not presented per woman randomized. Number of MII oocytes was presented per OPU and number of embryos and fertilization rate were restricted only to patients with ICSI.

A significantly higher number of follicles per woman starting treatment were retrieved in the corifollitropin alfa group compared with the rFSH group (4 RCTs; WMD 1.99, 95% CI 1.02–2.97; P=.11; moderate heterogeneity: I² = 50%).

A significantly higher number of MII oocytes per OPU were retrieved in the corifollitropin alfa group compared with the rFSH group (4 RCTs; WMD 1.92; 95% CI 1.25–2.59; P=.10; moderate heterogeneity: I² = 42%).

There was no evidence of a difference in total number of obtained embryos per woman with ICSI (4 RCTs; WMD 1.36; 95% CI 0.72–2.00; P=.64; no heterogeneity: I² = 0%) for corifollitropin alfa versus rFSH.

There were no significant differences in fertilization rate between groups (2 RCTs; WMD −1.34; 95% CI: −3.47 to 0.79; P=.60; I² = 0%).

Safety-Related Outcomes

OHSS incidence per woman randomized. OHSS was described in all four papers (Fig. 2C). The OHSS incidence varied from 5% to 6% in the corifollitropin alfa group and from 1% to 8% in the rFSH group (4 RCTs; OR 1.27, 95% CI 0.72–2.22; no heterogeneity: I² = 0%) with an absolute risk increase after corifollitropin alfa of 1%, assuming an OHSS control rate of 2%. The corresponding number needed to harm was 1.

Drug-related adverse events. Drug-related adverse events were clearly described in three papers. There was no evidence
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<td>Engage, 2009</td>
<td>Design: randomized, double-blind, double-dummy, active-controlled, noninferiority trial; international multicenter phase III trial (14 centers in North America and 20 centers in Europe. Patients: 1,506 women aged 18–36 y with body weight &gt;60 kg to 90 kg, BMI 18–32 kg/m², menstrual cycle length 24–35 d; exclusion criteria: endocrine abnormality, history of ovarian hyperresponse (&gt;30 follicles &gt;11 mm) or OHSS, PCOS, or basal AFC &gt;20 on ultrasound, or women with history of low ovarian response to FSH or hMG treatment, basal FSH or LH &gt;12 IU/L in early follicular phase, &gt;3 consecutive unsuccessful IVF cycles, smoking &gt;5 cigarettes per day.</td>
<td>Study group: single injection 150 µg (0.5 mL) corifollitropin alfa, SC + placebo for 7 d + ≤200 IU (from sd8) rFSH + GnRH antagonist (ganirelix, 0.25 mg) + 5,000–10,000 IU urinary hCG + P (≥600 mg/d vaginally or ≥50 mg/d IM. Control group: placebo + 200 IU rFSH (follitropin beta) + 200 IU (from sd8) rFSH + GnRH antagonist (ganirelix, 0.25 mg) + 5,000–10,000 IU urinary hCG + P (≥600 mg/d vaginally or ≥50 mg/d IM.</td>
<td>Ongoing pregnancy rate, no. of retrieved oocytes, dose of rFSH required, duration of stimulation, no. and size of follicles, serum hormone levels, fertilization rate, no. and quality of embryos obtained and pregnancy rates, and serious adverse events, i.e., ectopic pregnancy, missed abortion, pelvic pain, pelvic discomfort, headache, and drug-related local or systemic reactions.</td>
<td>Randomization (1:1 ratio) was done per center and stratified by age (&lt;32 and ≥32 y) by central remote allocation using randomly permuted blocks with an undisclosed fixed block size of 4. Concealed: yes. Sample size: yes. Blindness: double-blinded, double-dummy. ITT: yes. Funding: Schering-Plough.</td>
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<td>Ensure, 2010</td>
<td>Design: randomized, double-blind, double-dummy, equivalence trial; international multicenter phase III trial (14 centers in Europe and 5 centers in Asia. Patients: 396 women aged 18–36 y with body weight ≤60 kg, BMI 18–32 kg/m², menstrual cycle length 24–35 d; exclusion criteria: endocrine abnormality, history of ovarian hyper-response (&gt;30 follicles &gt;11 mm) or OHSS, PCOS, or basal AFC &gt;20 on ultrasound, or women with history of low ovarian response to FSH or hMG treatment, basal FSH or LH &gt;12 IU/L in early follicular phase, &gt;3 consecutive unsuccessful IVF cycles.</td>
<td>Study group: single injection 100 µg (0.5 mL) corifollitropin alfa SC + placebo for 7 d + ≤200 IU (from sd8) rFSH + GnRH antagonist (ganirelix, 0.25 mg) + 5,000–10,000 IU urinary hCG + P (≥600 mg/d vaginally or ≥50 mg/d IM. Control group: placebo + 200 IU rFSH (follitropin beta) + ≤200 IU (from sd8) rFSH + GnRH antagonist (ganirelix, 0.25 mg) + 5,000–10,000 IU urinary hCG + P (≥600 mg/d vaginally or ≥50 mg/d IM.</td>
<td>No. of cumulus-oocyte complexes retrieved, ongoing pregnancy rate, dose of rFSH required, dose of FSH after sd8, duration of stimulation, no. and size of follicles, serum hormone levels, fertilization rate, no. and quality of embryos obtained, implantation and pregnancy rates, and serious adverse events, i.e., ectopic pregnancy, missed abortion, pelvic pain, pelvic discomfort, headache, and drug-related local or systemic reactions.</td>
<td>Randomization: just before the start of stimulation. Randomization to one of the two treatment groups in a 2:1 ratio was performed at each center and stratified by age (&lt;32 or ≥32 y) and by central remote allocation using randomly permuted blocks with an undisclosed fixed block size of 3. Concealed: yes. Sample size: yes. Blindness: double-blinded, double-dummy. ITT: yes. Funding: Schering-Plough.</td>
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<td>Corifollitropin Alfa Dose-Finding Study Group, 2008</td>
<td>Design: multicenter, open-label, randomized phase II study with three doses of corifollitropin alfa (60, 120, and 180 mg) in a COS regimen for IVF or ICSI. Patients: 325 women aged 20–39 y with a normal menstrual cycle (24–35 d) and BMI 17–31 kg/m²; exclusion criteria: history of OHSS, PCOS, or any endocrine abnormality, previous poor response to FSH or hMG, &gt;3 unsuccessful COS cycles, &lt;2 ovaries, abnormal hormone levels during days 2–7 of menstrual cycle, use of hormonal preparations within 1 month before treatment or previous use of corifollitropin alfa.</td>
<td>Study group: single injection of 60, 120, or 180 µg corifollitropin alfa SC + 150 IU (from sd8) rFSH (follitropin beta) + GnRH antagonist (ganirelix, 0.25 mg) + 10,000 IU hCG + progesterone. Control group: 150 IU rFSH (follitropin beta) + GnRH antagonist (ganirelix, 0.25 mg) + 10,000 IU hCG + P.</td>
<td>No. of cumulus-oocyte complexes retrieved, no. of follicles and E2 levels on sd8, dose of rFSH required, no. and size of follicles, serum hormone levels, fertilization rate, no. and quality of embryos obtained and transferred, and pregnancy rates.</td>
<td>Randomization (1:1:1:1 ratio) was stratified by age (&lt;32 or ≥32 y) and by center using a central remote allocation procedure using a fixed block size of 4 and a minimization algorithm combined with randomly permuted blocks. Concealed: yes. Sample size: yes. Blindness: open-label. ITT: yes. Funding: Organon.</td>
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<td>Devroey et al., 2004</td>
<td>Design: open-label randomized four-arm phase II trial. Patients: 99 women aged 18–39 y, BMI 18–29 kg/m², with a regular menstrual cycle (24–35 d); exclusion criteria not reported clearly.</td>
<td>Study group: a single SC dose of FSH-CTP (corifollitropin alfa) of 120 (n = 25), 180 (n = 24), or 240 (n = 25) µg + 150 IU (from sd8) rFSH + GnRH antagonist (ganirelix, 0.25 mg) + 10,000 IU urinary hCG + vaginal micronized P (600 mg/d) or IM P (≥50 mg/d). Control group: 150 IU (from sd8) rFSH + GnRH antagonist (ganirelix, 0.25 mg) + 10,000 IU urinary hCG + vaginal micronized P (600 mg/d) or IM progesterone (≥50 mg/d).</td>
<td>rFSH dose needed from sd 8 onward, duration of stimulation, no. of oocytes, MII oocytes, fertilization rate, no. of embryos, and ongoing pregnancy rate.</td>
<td>Randomization: yes, but method of randomization not reported. Concealed: unclear. Sample size: yes. Blindness: open-label. ITT: yes. Funding: Organon.</td>
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Note: AFC = antral follicle count; BMI = body mass index; COS = controlled ovarian stimulation; CTP = C-terminal peptide; IM = intramuscular; ITT = intention to treat; MII = metaphase II; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome; SC = subcutaneous; sd8 = stimulation day 8.

of statistically significant difference between groups (3 RCTs; OR 1.11, 95% CI 0.75–1.63; P = .57; no heterogeneity: I² = 0%). There was no evidence of a difference in multiple pregnancy between groups (4 RCTs; OR 1.20, 95% CI 0.90–1.67; P = .73; no heterogeneity: I² = 0%).

Cancellation rate per woman randomized. The total cancellation rate due to causes such as low or high response was significantly higher in the corifollitropin alfa group (4 RCTs; OR 1.47, 95% CI 1.08–2.02; P = .76; no heterogeneity: I² = 0%). This cancellation rate was due to a high ovarian response in the corifollitropin alfa group compared with the rFSH group (2 RCTs; OR 5.67, 95% CI 1.07–30.13) and a low ovarian response in both groups (2 RCTs; OR 1.14, 95% CI 0.72–1.81).

DISCUSSION
To the best of our knowledge, the present systematic review and meta-analysis presents the most recent evidence summarizing randomized controlled trials comparing a single dose of corifollitropin alfa with daily recombinant rFSH in women undergoing IVF. Corifollitropin alfa has an approximately twofold longer elimination half-life and an almost fourfold extended time interval compared with rFSH (2). Because of these pharmacokinetic characteristics, it was anticipated that a single injection of corifollitropin alfa may have the same safety and efficacy as a daily rFSH regimen but might lower the treatment burden of women undergoing COS.

This meta-analysis indeed suggests that combination of corifollitropin with fixed daily GnRH antagonist injections starting on stimulation day 5 seems to yield similar pregnancy rates, as well as significantly higher numbers of oocytes, MII oocytes, and obtained embryos and less amount of used FSH compared with women stimulated with daily rFSH injections. The median duration of stimulation with FSH was 9 days in both treatment groups, which means that, on average, recipients of corifollitropin alfa and daily rFSH required only two further days of stimulation.
stimulation with rFSH before final oocyte maturation triggering.

However, corifollitropin alfa was associated with a higher cycle cancellation rate than daily rFSH, which may have more psychologic impact on patients than the benefit of fewer injections associated with corifollitropin alfa (26). The risk of cancellations due to high ovarian response and high risk to develop OHSS was fivefold higher in the corifollitropin alfa group than in the rFSH group. Even so, there was only a tendency to more cases of OHSS in the corifollitropin alfa group compared with the rFSH group (3% vs. 2%), and the differences were not statistically significant. The incidence of moderate/severe OHSS in corifollitropin alfa was increased by almost 50% in the corifollitropin alfa group compared with the rFSH group. The higher ovarian response and the risk of OHSS in corifollitropin alfa group could be explained by the sustained and higher FSH immunoreactivity concentrations and the inability for dose adjustment after treatment with a single dose of corifollitropin compared with the daily rFSH regimen (where the dose can be adjusted according to the ovarian response to avoid low or high ovarian response), leading to a rapid increase of serum E2 and inhibin levels and
development of more medium-size follicles (11–14 mm) with corifollitropin alfa on day 8 (7.8% vs. 6.4%) and day of hCG (6.4% vs. 5.2%) (5, 12, 27). It should be taken into consideration that women participated in the included studies were normal responders, so the ovarian response and OHSS incidence in women with polycystic ovary syndrome or women at higher risk to develop OHSS may overwhelm these observations.

Also, we found more multiple pregnancies in the corifollitropin alfa group (113/1341 and 78/1099) compared with the daily rFSH group (78/985 and 49/902), although the differences were not statistically significant. Corifollitropin alfa was well tolerated and nonimmunogenic (5, 9); there was no significant difference between corifollitropin alfa and rFSH regarding the most commonly reported side effects, such as pelvic pain, pelvic discomfort, headache, and drug-related

Forest plot showing (A) pregnancy outcomes per woman, (B) randomized ovarian stimulation outcomes, (C) safety-related outcomes in daily rFSH and corifollitropin alfa groups.

local or systemic reactions, but in view of the cancellation rates and OHSS rates, these data are of limited clinical value.

The overall methodologic quality of the trials was good, and they were published as full manuscripts in peer-reviewed journals. The method of allocation with the use of computer-generated randomization or sealed envelopes was reported in all studies. Two studies were double-blind double-dummy; the other two were open-label, which might be a potential source of bias that could have yielded exaggerated estimates of corifollitropin alfa effect. Sample size calculations and intention-to-treat analyses were performed in all studies. One study was conducted in a single center, and three were multicenter studies. There was clinical heterogeneity between trials in the type of patients (were multicenter studies. There was clinical heterogeneity between trials in the type of patients (were multicenter studies. One study was conducted in a single center, and three were multicenter studies. There was clinical heterogeneity between trials in the type of patients (were multicenter studies. One study was conducted in a single center, and three were multicenter studies. There was clinical heterogeneity between trials in the type of patients (were multicenter studies. One study was conducted in a single center, and three were multicenter studies. There was clinical heterogeneity between trials in the type of patients (were multicenter studies. One study was conducted in a single center, and three were multicenter studies. There was clinical heterogeneity between trials in the type of patients (were multicenter studies. One study was conducted in a single center, and three were multicenter studies. There was clinical heterogeneity between trials in the type of patients.

Heterogeneity may generate misleading results, but the results were consistent across the trials and there was no significant alteration in results in most outcomes between fixed- and random-effects models used to evaluate the possible effect of heterogeneity.

Although an increased risk of corifollitropin alfa–related complications for the fetus or newborn has not been demonstrated (12–14, 27, 28), studies on the long-term outcome of corifollitropin alfa pregnancies are lacking. It is therefore currently unknown whether the child or mother may experience any consequences later in life. Corifollitropin alfa is not preferred in long agonist cycles, because a larger cohort of follicles is expected with a higher risk of OHSS and as a consequence possibly high cancellation rates (15, 29).

Clinically, the main problem with corifollitropin alfa is that no dose adjustments can be made in patients with a low response or in patients with a risk of high response, such as women with polycystic ovary syndrome. As such, corifollitropin alfa is not a patient-friendly treatment option, although studies evaluating patients’ preference, comfort, and compliance with corifollitropin alfa compared with standard daily FSH are lacking. Alternative strategies to avoid cycle cancellations due to OHSS may therefore be explored further. For example, a GnRH agonist could be used to replace hCG for final oocyte maturation triggering in GnRH antagonist down-regulated cycles (30). Also, middle to late follicular phase initiation of low-dose exogenous long-acting corifollitropin alfa plus GnRH antagonist as a mild stimulation strategy might induce dominant follicle development without increasing the risk of OHSS and cycle cancellation.

In conclusion, in view of its equivalence and safety profile, corifollitropin alfa in combination with daily GnRH antagonist seems to be an alternative for daily rFSH injections in normal-responder patients undergoing ovarian stimulation in IVF/ICSI treatment cycles.

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